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| EXAMINER | |
|---|---|
| GOLDBERG,J | |
| ART UNIT | PAPER NUMBER |
| 1655 | 7 |

DATE MAILED: 09/13/00

**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents and Trademarks**

| Office Action Summary | Application No. 09/485,879 | Applicant(s) GIESING ET AL. | |
|---|---|---|---|
| | Examiner Jeanine A Enewold Goldberg | Art Unit 1655 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

**Status**

1)☒ Responsive to communication(s) filed on *12 July 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. § 119**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of the CERTIFIED copies of the priority documents have been:

1.☐ received.

2.☐ received in Application No. (Series Code / Serial Number) _____ .

3.☐ received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

**Attachment(s)**

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

## DETAILED ACTION

### *Priority*

1. This application is a 371 of PCT/EP/98/05360, filed August 24, 1998. This application also claims priority to foreign document 197 36 691.0, filed August 24, 1998, however, a translation of this document has not been provided.

### *Specification*

2. The abstract of the disclosure is objected to because the abstract contains more than 250 words. Correction is required. See MPEP § 608.01(b).

### *Claim Objections*

Claims 6-13 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent Claim 6 depends upon additional multiple dependent claim 5. See MPEP § 608.01(n). Accordingly, the claims 6-13 have not been further treated on the merits.

### *Claim Rejections - 35 USC § 101*

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

3. Claims 14-15 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Claims 14 and 15 are directed to Claims reciting "the use".

Claims 14 and 15 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 1-17 are indefinite because the claims do not recite a positive process step which clearly relates back to the preamble. The preamble states that the method is for the multiple characterization of disseminated and micrometastasized cancer cells but the final process step is investigating at least one cancer specific gene. Therefore the claims are unclear as to whether the method is a method of multiple characterization of disseminated and micrometastasized cancer cells or investigating at least one cancer specific gene. The claims are unclear exactly what the method steps entail.

B) Claims 1-17 are indefinite because it is unclear because the claims recites obtaining cells from body fluid and investigating for at least one cancer-specific gene

based upon mRNA and the subsequently recites removing cancer cells from the body fluid and investigating for at least one cancer-specific gene on the basis of DNA and/or mRNA. It is unclear whether these two method steps are distinct or whether the cells obtained from the single body fluid sample are investigated based upon mRNA or whether there are two different body fluid samples, or whether one of the samples is infact a tumor which knowingly has cancer cells, or whether the first recited sample is then examined for cancer cells. Thus, the metes and bounds of the claimed invention are unclear.

C) Claims 1-17 are unclear based upon the recitation "multiple characterization of disseminated and micrometastasized cancer cells" because it is unclear whether many (multiple) cancer cells are characterized, or whether multiple genes are characterized within cancer cells or whether a single gene is characterized in multiple ways such as expression, structure (mutations) and function. Thus, it is unclear the metes and bounds of the claimed invention.

D) Claim 2-3, 5, 6-13 are indefinite over the recitation in claim 2, "analyses on the basis of mRNA are carried out on those cancer-specific genes which are essentially not expressed in non-cancer cells in the body fluid investigated" because it is unclear what constitutes a "cancer-specific gene which is essentially not expressed in non-cancer cells".

E) Claim 4 is indefinite over the recitation "the genomic DNA" because it is unclear how this limitation relates to Claim 1 since Claim 1 does not recited genomic DNA. Thus, genomic DNA lacks proper antecedent basis.

F) Claims 6-13 are indefinite over the recitation "investigated" because it is unclear what the metes and bounds of "investigate" entail. It is unclear whether the mere presence of a gene constitutes investigation, or whether further analysis such as determination of copy number, possible aberrations are required to meet the limitation of investigation. Furthermore, it is unclear whether two cancer-associated genes are analyzed or whether the cancer-specific gene is merely investigated in Claim 6.

G) Regarding claims 8-13, the phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d). Claim 8 recites matrix degradation factors such as proteinases and their inhibitors, and/or adhesion factors such as adherins.

H) Claim 12 is indefinite over the recitation "are also investigated singly" because it is unclear the extent of "investigated". It is unclear whether certain characteristics are investigated or whether investigated implies that the same characterization is determined for the single cell. It is unclear what the metes and bounds of the claimed invention entail.

I) Claims 14 and 15 provides for the use of the method according to any of Claims 1-13, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass.

A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

J) Claims 16 and 17 are indefinite over the recitation "means for carrying out the method" because it is unclear whether the means are the products, primers, probes and controls or whether the means for carrying out the method are drawn to apparatus and or such. It is unclear whether these claims are kits or whether these claims are the machines or whether these claims are drawn to something entirely distinct.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

5. Claims 1-3, 6-7, 9, 13-17 are rejected under 35 U.S.C. 102(b) as being anticipated by Selby et al (WO 96/17080, June 1996).

Selby et al. (herein referred to as Selby) teaches a method of detecting disseminated and micrometasstasized cancer cells by obtaining a sample of tissue from a patient and analyzing DNA and/or RNA (limitations of Claim 1). Selby teaches that CK20 gene is not expressed in normal blood samples, but CK20 is express in a high

proportion of colorectal carcinomas, stomach cancers, mucinous ovarian adenocarcinomas and transitional cell carcinomas (limitations of Claim 2 and 3)(pg 4, lines 18-22). Selby teaches that the presence of cytokeratin 20 gene may be determined by detecting CK20 mRNA (pg. 7, lines 15-20)(limitations of Claim 9). Selby also teaches kits comprising primers for amplifying CK20 cDNA (limitations of Claim 16 and 17)(pg 13).

6. Claims 1-6, 9, 13-16 are rejected under 35 U.S.C. 102(b) as being anticipated by Pantel et al (Onkology, Vol 18, pg 394-401, 1995).

Pantel et al. (herein referred to as Pantel) teaches a method of detecting disseminated and micrometasstasized cancer cells by obtaining a sample of tissue from a patient and analyzing DNA and/or RNA (limitations of Claim 1). Pantel teaches that PCR-basded methods are applied to detect tumor-associated mutations of the ki-ras and p53 genes or mRNA from 'tissue-specific' genes (abstract)(limitations of Claims 2 and 4). Pantel explicitly states that two PCR-based methods of detecting micrometastic cells are (a) those that detect altered DNA in the form of mutations or rearrangements and (b) those that use RT-PCR to detect mRNA from tissue specific genes (pg. 397, col. 2). The unique genomic characteristics such as chromosomal translocations or idiotypic rearrangements of these genes are noted. Single base mutations in the K-ras gene are noted (pg 398, col 1)(limitations of Claims 4-5, 7-8). Pantel also teaches CEA is studied as marker mRNA (Table 2)(Limitations of Claim 3). CEA was not found in mRNA samples of normal bone marrow and peripheral blood (limitations of Claim 2, 7, 9).

7. Claims 1-3, 6, 7, 9, 14-15 are rejected under 35 U.S.C. 102(b) as being anticipated by Jung et al (Eur. J. of Clinical Chemistry and Clinical Biochemistry, Vol. 35, No. 1, pg. 3-10, January 1997).

Jung et al. (herein referred to as Jung) teaches a method of characterizing disseminated and micrometastasized cancer cells by RT-PCR (limitations of Claim 1). Jung teaches using RT-PCRs specific for CEA, PSA and CK18 to systematically investigate specimens for a number of factors that contribute to the varying and seemingly implausible test results. Jung teaches that "the prerequisite for translating the results from highly sensitive and specific RT-PCR assays into clinically relevant data is the thorough definition of assay procedures and the number of tests performed on a sample" (abstract). Jung teaches tyrosinase is most frequently investigates for the detection of melanoma cells and PSA for prostate cancers (pg. 3-4). As seen in Table 1, **CEA, CK20, MUC1, tryonsinase and MAGE3** genes have detected micrometastasis in human solid tumors by reverse transcriptation polymerase reaction (limitations of Claim 2 and 3)(pg. 4). Jung teaches detecting mRNA of CK20.

8. Claims 1, 4-10 are rejected under 35 U.S.C. 102(b) as being anticipated by Schmitz-Drager et al (World J. Urol, Vol 14, pg 190-196, 1996).

Schmitz-Drager et al. (herein referred to as Schmitz-Drager) teaches several oncogenes which are involved in the specific steps of tumor progression and dissemination have been identified, for example the epithelial growth factor receptor

(EGF-R) and tumor-suppressor genes, such as p53 (abstract)(limitations of Claim 4). Schmitz-Drager teaches that "a correlation between p53 inactivation and dissemination" exists (pg 192, col 1)(limitations of Claim 4). Additionally, Schmitz-Drager teaches that "a significant correlation found between a loss of RB expression and survival within all patients examined as well as among the group of patients with invasive bladder tumors signals a higher metastatic potential for tumors with compromised RB expression (limitations of Claim 4 and 5). Schmitz-Drager teaches that mRNA from vascular endothelial growth factor (VEGF) is a strong inducer of microvascular hyperpermeability (pg 193, col 1)(limitations of Claims 9-10).

9. Claims 1-3, 6-7, 9, 11, 13-16 are rejected under 35 U.S.C. 102(b) as being anticipated by Noguchi et al (Cancer, Vol. 74, No 5, pg. 1595-1600, 1994).

Noguchi et al. (herein referred to as Noguchi) teaches a method for detecting breast carcinoma micrometastases by RT-PCR. MRNA from MCU1 was extracted from breast carcinoma cell line, primary breast carcinomas, and axillary lymph notes for analysis (abstract)(limitations of Claims 1). Noguchi teaches that MUC1 was uniformly and highly expressed in breast carcinomas, and rarely expressed in nonepithelial tissues (og 1596, col 1)(limitations of Claim 2 and 3). Specifically the method characterizes MUC1 mRNA expression (limitations of Claim 9). The RNA extraction method included centrifugation (limitations of Claim 11). Noguchi assets that "MUC1 RT-PCR methods is so sensitive that it can detect breast carcinoma micrometastases in lymph nodes that cannot be detected by immunohistochemistry" (pg 1600, col 1).

10. Claims 1-4, 6-9, 12-16 are rejected under 35 U.S.C. 102(b) as being anticipated by Pelkey et al (Clinical Chemistry, Vol. 42, No. 9, pg. 1369-1381, 1996).

Pelkey et al. (herein referred to as Pelkey) teaches the characterization of disseminated and micrometastasized cancer cells on the basis of DNA wherein cells obtained from body fluid are investigated for at least one cancer-specific gene. Specifically, Pelkey teaches using RT-PCR to detect micrometastases in which cells are extracted from blood, bone marrow, lymph node by cytocentrifugation techniques (pg 1373, col 1). Pelkey also teaches extracting mRNA to study amplification of tyrosinase (limitations of Claim 9)(pg 1374, col 1). Moreover, "detection of the micrometastases of melanoma in peripheral blood was increase by amplification of four melanoma-associated gene markers (tyrosinase, p97, MUC18 and MAGE-3) (limitations of Claims 2 and 3)(pg. 1374, col. 2). Pelkey also teaches studying numerous molecular and cellular abnormalities including p53 mutations Limitations of Claim 4)(pg. 1375, col. 1).

***Conclusion***

**11. No claims allowable over the art.**

**12.** The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

A) Pittman et al (Annals of Oncology, Vol. 7, pg. 297-301, 1996) teaches tyrosinase mRNA detecting metatstic malignant melanoma.

B) Burchill et al (Br. J. of Cancer, Vol. 71, pg. 278-281, 1995) teaches CK 20 for detection of metastasis.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Enewold Goldberg whose telephone number is (703) 306-5817. The examiner can normally be reached Monday-Thursday from 7:00AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305- 3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Jeanine Enewold Goldberg
September 5, 2000 JE

Lisa B. Arthur

LISA B. ARTHUR
PRIMARY EXAMINER
GROUP ~~1800~~ 1600